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BINDER 1

x	D1	EP 0 005 129 A1
x	D2	EP 0 124 495 A2
x	D3	DE 40 35 455 A1
	D4	J. March, Advanced Organic Chemistry, 4 th edition, 1992, John Wiley & Sons, pages 100, 120/121 and 378/379"
	D5	A. Pilbrant, C. Cederberg, Development of an oral formulation of omeprazole, Scandinavian Journal of Gastroenterology, 1985, 20, 113-120
	D6	Beyer, Walter, Lehrbuch der Organischen Chemie [Textbook of organic chemistry], 1991, S. Hirzel Verlag, Stuttgart, 22 nd edition, pages 735-6.
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	D11	Methoden der Organischen Chemie (Houben Weyl) [Methods of organic chemistry, Houben Weyl], volume I/1, 1958, chapter "Crystallization", pages 345-389.
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	D14	P Erlandsson <i>et al.</i> , in Journal of Chromatography 532 (1990) 305-319.
	D15	W. Forth <i>et al.</i> : " <i>Allgemeine und spezielle Pharmakologie und Toxikologie</i> " [General and special pharmacology and toxicology], Wissenschaftsverlag, 6 th edition 1992, pages 33/34, 55-57, 70 and 472/473.
	D16	M. Eichelbaum <i>et al.</i> Klin. Wochenschr. 1980 Sep 15;58(18): Abstract.
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	D 24	Extract from Comprehensive Medicinal Chemistry, page 205.
	D25	Renberg <i>et al.</i> Drug Metabolism and Disposition (1989) 69.
	D26	Abstract conference 19-22 September 1993

D1



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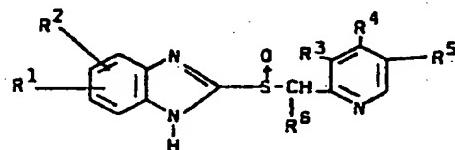
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(56) Substituted pyridylsulfanylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.

(57) The present invention relates to novel compounds of the formula



A1 wherein R¹ and R² are same or different and are each hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, or alkanoyl, R⁶ is hydrogen, methyl or ethyl, R³, R⁴ and R⁵ are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy whereby R³, R⁴ and R⁵ are not all hydrogen, and whereby when two of R³, R⁴ and R⁵ are hydrogen the third of R³, R⁴ and R⁵ is not methyl. The compounds are potent gastric acid secretion inhibitors.

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UI/LB/EMH

Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

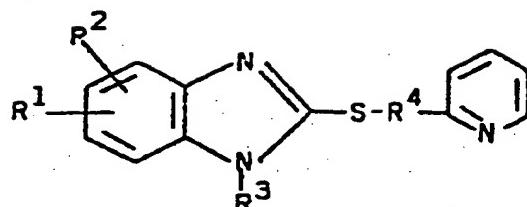
The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man, as well as the process for their preparation, method of affecting gastric acid secretion
5 and pharmaceutical preparations containing said novel compounds.

The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit
10 exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

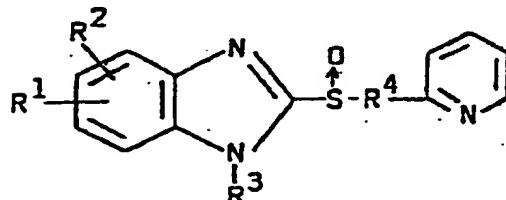
It is previously known that compounds of the formulas I and II

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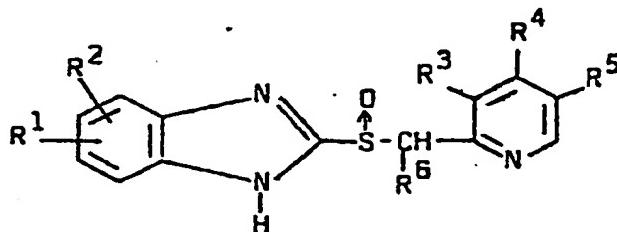
- wherein R^1 and R^2 are each selected from the group consisting of hydrogen, alkyl, halogen, cyano, carboxy, carboxy-
 15 alkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoyl-
 oxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl and
 acyl in any position, R^3 is selected from the group con-
 sisting of hydrogen, alkyl, acyl, carboalkoxy, carbamoyl,
 alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl,
 20 alkoxycarbonylmethyl, and alkylsulphonyl, and R^4 is selected
 from the group consisting of straight and branched alkylene
 groups having 1 to 4 carbon atoms, whereby at most one
 methylene group is present between S and the pyridyl group,
 and whereby the pyridyl group may be further substituted
 25 with alkyl or halogen, possess inhibiting effect of gastric
 acid secretion.

- It has now, however, surprisingly been found that the
 compounds defined below possess a still greater inhibiting
 30 effect than those given above.

Compounds of the invention are those of the general formula

III

35



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wherein R¹ and R² are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R⁶ is selected from the group consisting of hydrogen, methyl, and ethyl,
5 and R³, R⁴ and R⁵ are same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy, and ethoxyethoxy whereby R³, R⁴, and R⁵ are not all hydrogen, and whereby when two of R³, R⁴, and R⁵ are hydrogen, the third of R³, R⁴ and R⁵ is not methyl.

10

Alkyl R¹ and R² of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl; n-butyl
15 or isobutyl.

Halogen R¹ and R² is chloro, bromo, fluoro, or iodo.

Alkoxy R¹ and R² are suitably alkoxy groups having up to 5
20 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

Alkanoyl R¹ and R² have preferably up to 4 carbon atoms and are e.g. formyl, acetyl, or propionyl, preferably acetyl.

25

A preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl, whereby R¹ and R²
30 are not both hydrogen, R⁶ is hydrogen, and R³, R⁴, and R⁵ are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R³, R⁴, and R⁵ are not all hydrogen, and whereby when two of R³, R⁴, and R⁵ are hydrogen the third of R³, R⁴,
35 and R⁵ is not methyl.

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A second preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl.

5 R⁶ is selected from the group consisting of hydrogen, methyl, and ethyl, R³ is methyl, R⁴ is methoxy, and R⁵ is methyl.

A third preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different
10 and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R⁶ is selected from the group consisting of hydrogen, methyl and ethyl, and R³ is hydrogen, R⁴ is methoxy and R⁵ is methyl or R³ is methyl, R⁴ is methoxy and R⁵ is hydrogen.

15 A fourth preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,
20 R⁶ is selected from the group consisting of hydrogen, methyl and ethyl, R³ and R⁵ are hydrogen and R⁴ is methoxy.

A fifth preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different
25 and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R⁶ is selected from the group consisting of hydrogen, methyl and ethyl, and R³ and R⁵ are methyl and R⁴ is hydrogen.

30 A sixth preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl,
35 R⁶ is selected from the group consisting of hydrogen, methyl and ethyl, R³ and R⁵ are hydrogen and R⁴ is ethoxy, methoxyethoxy or ethoxyethoxy.

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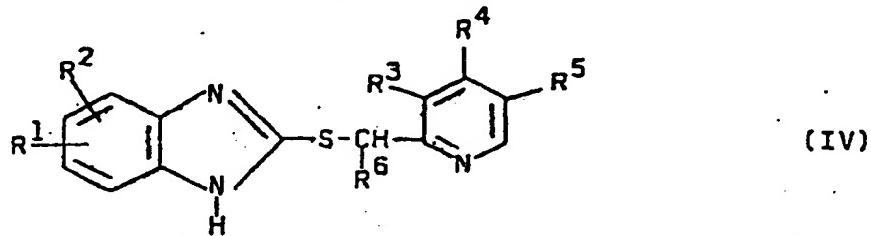
A seventh preferred group of compounds of the general formula III are those wherein R¹ and R² are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy, and S alkanoyl, R⁶ is selected from the group consisting of hydrogen, methyl, and ethyl, R³, R⁴, and R⁵ are all methyl.

Compounds of formula III above may be prepared according to the following methods:

10

a) oxidizing a compound of formula IV

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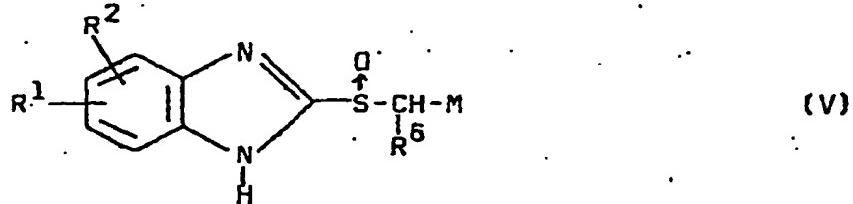


20

wherein R¹, R², R⁶, R³, R⁴, and R⁵ have the meanings given, to the formation of a compound of formula III.

b) reacting a compound of the formula V

25



30

wherein R¹, R², and R⁶ have the meanings given above and M is a metal selected from the group consisting of K, Na and Li, with a compound of formula VI.

35

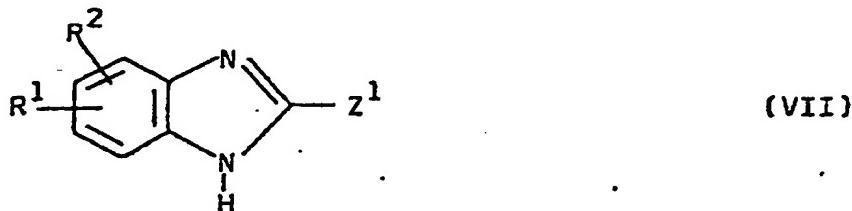


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wherein R³, R⁴, and R⁵ have the same meanings as given above, Z is a reactive esterified hydroxy group, to the formation of a compound of formula III;

5 c) reacting a compound of the formula VII

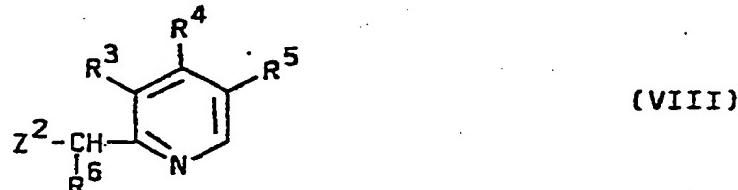
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15

wherein R¹, and R² have the same meanings as given above and Z¹ is SH or a reactive esterified hydroxy group, with a compound of the formula VIII

20

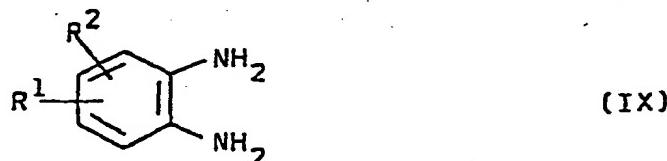


25

wherein R⁶, R³, R⁴, and R⁵ have the same meanings as given above, and Z² is a reactive esterified hydroxy group or SH, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III;

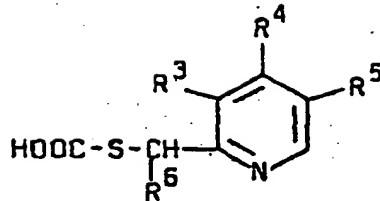
d) reacting a compound of the formula IX

30



35

wherein R¹ and R² have the same meanings as given above with a compound of the formula X



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(X)

5

wherein R⁶, R³, R⁴, and R⁵ have the same meanings as given above, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula
 10 III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z¹, and Z² may be a reactive, esterified hydroxy group which is a hydroxy group esterified
 15 with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzene-sulfonic acid, 4-bromobenzenesulfonic acid or 4-toluene-sulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent selected from the group consisting of nitric acid,
 25 hydrogen peroxide, peracids, peresters, ozone, dinitrogen-tetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazobicyclo-[2.2.2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfonyl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

35 Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or or mixed salts may be obtained as well as hemi-, mono-, sesqui-

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- or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may 5 form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, 10 heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, 15 embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.
- 20 These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship 25 between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.
- Some of the new compounds may, depending on the choice of 30 starting materials and process, be present as optical isomers or racemate, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).
- 35 The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystal-

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lization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95 % by weight of the preparation, between 0.5 to 20 % by weight in preparations for injection and between 2 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an anti-friction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed

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- into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.
- 5 10 Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.
- 15 Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance 20 in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.
- 25 30 Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2 % to 20 % by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, 35 flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.
- Solutions for parenteral administration by injection may be 35 prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 % to 10 % by weight. These solutions may also contain stabilizing agents and/or

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buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20,000 to 200,000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates a preferred embodiment of the invention without being limited thereto. Temperature is given in degrees Centigrade.

- 5 The starting materials in the examples found below were prepared in accordance with the following methods:
(1) a 1,2-diamino compound, such as α -phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptopbenzimidazole;
- 10 (2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448-451 (1956));
(3) the compound 2-chloromethylbenzimidazole was prepared by condensing α -phenylenediamine with chloroacetic acid.

15

Example 1

- 28.9 g of 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)-benzimidazole were dissolved in 160 ml of CHCl_3 .
- 20 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with CH_2Cl_2 , washed with Na_2CO_3 solution, dried over Na_2SO_4 and evaporated in vacuo. The residue
- 25 crystallized when diluted with CH_3CN , and 2-[2-(4,5-di-methyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole was recrystallized from CH_3CN . Yield 22.3 g; m.p. 158°C.

30 Examples 2-30

The preparation of compounds of formula III labelled 2-26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table I which identifies
35 the substituents for these compounds.

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Example 31 (method c)

- 0.1 moles of 4-6-dimethyl-2-mercaptopbenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 5 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue was dissolved in acetone and was treated 10 with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl)pyridylmethylthio]-(4,6-dimethyl)benzimidazole was isolated. Yield 0.05 moles.
- 15 This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound melting point 50-55°C.

Example 32 (method b)

- 20 0.1 moles of 2-[Li-methylsulfinyl](5-acetyl-6-methyl)-benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was 25 filtered off, and the solution was evaporated in vacuo. The residue was crystallized from CH₃CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole melting at 171°C.

Example 33 (method d)

- 30 23.4 g of 2-[2-(3,4,5-trimethyl)pyridylmethylthio].formic acid and 16.6 g of α-(5-acetyl-6-methyl)phenylenediamine were 35 boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was

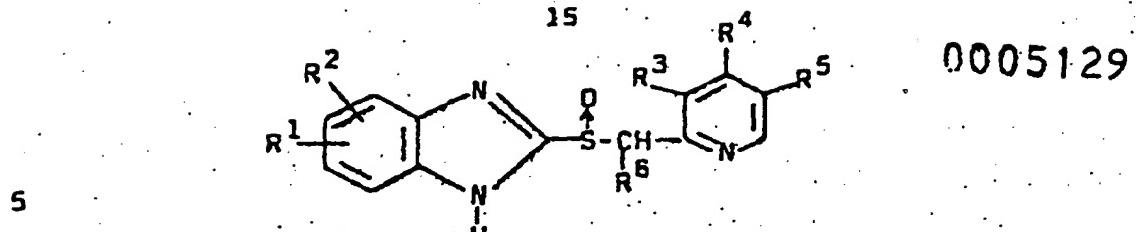
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treated with active carbon and evaporated in vacuo. The residue was dissolved in acetone wheresupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was 5 recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-(5-acetyl-6-methyl)benzimidazole was 6.5 g.

This compound was then oxidized in accordance with Example 1
10 above, to give the corresponding sulfinyl derivative.
M.p. 190°C.

Example 34 (method c)

- 15 22.0 g of 2-mercapto-(5-acetyl-6-methyl)benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95 % ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed 20 was filtered off and the solution was evaporated in vacuo. The residue, 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole, was recrystallized from 70 % ethanol. Yield 10.6 g.
- 25 This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative.
M.p. 158°C.

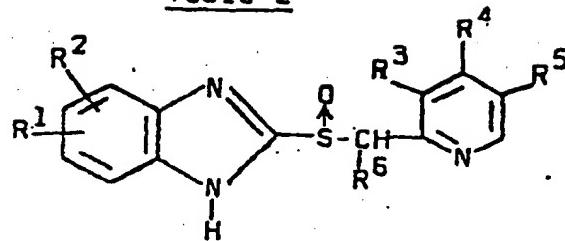


Ex.	R ¹	R ²	R ⁶	R ³	R ⁴	R ⁵	M.p. °C	
10								
1	S-COCH ₃	6-CH ₃	H	H	CH ₃	CH ₃	158	
2	S-COOCH ₃	6-CH ₃	H	H	CH ₃	CH ₃	163	
3	S-COOCH ₃	H	H	H	CH ₃	CH ₃	141	
15	4-CH ₃	6-CH ₃	H	CH ₃	CH ₃	H	160	
4	S-COCH ₃	6-CH ₃	H	CH ₃	CH ₃	H	163	
5	S-COOCH ₃	6-CH ₃	H	CH ₃	CH ₃	H	163	
6	4-CH ₃	6-CH ₃	H	CH ₃	H	CH ₃	50-55	
7	S-COCH ₃	6-CH ₃	H	CH ₃	H	CH ₃	171	
8	S-COCH ₃	6-CH ₃	H	CH ₃	CH ₃	CH ₃	190	
20	9	S-COCH ₃	6-CH ₃	H	H	OCH ₃	H	165
10	4-CH ₃	6-CH ₃	H	H	OCH ₃	H	122	
11	S-COCH ₃	6-CH ₃	H	CH ₃	OCH ₃	CH ₃	156	
12	S-COOCH ₃	6-CH ₃	H	CH ₃	H	CH ₃	144	
13	S-COOCH ₃	6-CH ₃	H	CH ₃	CH ₃	CH ₃	185	
25	14	S-COOCH ₃	6-CH ₃	H	H	OCH ₃	H	169
15	S-COOCH ₃	6-CH ₃	H	H	OCH ₂ H ₅	H	148	
16	S-COOCH ₃	6-CH ₃	H	CH ₃	OCH ₃	H	175	
17	S-COOCH ₃	6-CH ₃	H	CH ₃	OCH ₃	CH ₃	155	
18	S-COOCH ₃	6-CH ₃	H	H	OCH ₃	CH ₃	158	
30	19	S-COOCH ₃	H	H	CH ₃	H	CH ₃	141
20	S-COOCH ₃	H	H	CH ₃	OCH ₃	CH ₃	142	
21	S-COCH ₃	H	H	CH ₃	OCH ₃	CH ₃	162	
22	S-OCH ₃	H	H	H	OCH ₃	CH ₃	178	
23	S-OCH ₃	H	H	CH ₃	OCH ₃	CH ₃	156	
35	24	S-CH ₃	H	H	CH ₃	OCH ₃	CH ₃	181
25	H	H	H	CH ₃	OCH ₃	CH ₃	165	
26	S-Cl	H	H	CH ₃	OCH ₃	CH ₃	185	
27	S-CH ₃	H	H	H	OC ₂ H ₄ OCH ₃	H	119	
28	S-COOCH ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃	150-5	
29	S-COOCH ₃	H	CH ₃	CH ₃	H	CH ₃	130	
30	S-CH ₃	H	CH ₃	CH ₃	H	CH ₃	152	

Biological effect

- The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed on conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administration of the test compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1-4 nmol/kg, h) lasting for 6-7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol H⁺/60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, -suspended in 0.5 % Methocel® (methyl cellulose), were given intraduodenally in doses from 4-20 µmol/kg when the secretory response to pentagastrin has reached a steady level.
- In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.
- The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Table 2



Ex.	R ¹	R ²	R ⁶	R ³	R ⁴	R ⁵	Dose	Effect
							μmol/kg	% inhibition
10	1	5-COCH ₃	6-CH ₃	H	H	CH ₃	CH ₃	2
	4	5-COCH ₃	6-CH ₃	H	CH ₃	CH ₃	H	1
	7	5-COCH ₃	6-CH ₃	H	CH ₃	H	CH ₃	2
	8	5-COCH ₃	6-CH ₃	H	CH ₃	CH ₃	CH ₃	4
	9	5-COCH ₃	6-CH ₃	H	H	OCH ₃	H	2
	11	5-COCH ₃	6-CH ₃	H	CH ₃	OCH ₃	CH ₃	0.5
	x	5-COCH ₃	6-CH ₃	H	H	CH ₃	H	20
	x	5-COCH ₃	6-CH ₃	H	H	H	CH ₃	8
20	2	5-COOCH ₃	6-CH ₃	H	H	CH ₃	CH ₃	2
	5	5-COOCH ₃	6-CH ₃	H	CH ₃	CH ₃	H	2
	12	5-COOCH ₃	6-CH ₃	H	CH ₃	H	CH ₃	2
	13	5-COOCH ₃	6-CH ₃	H	CH ₃	CH ₃	CH ₃	4
	14	5-COOCH ₃	6-CH ₃	H	H	OCH ₃	H	2
25	15	5-COOCH ₃	6-CH ₃	H	H	OCH ₂ CH ₃	H	4
	16	5-COOCH ₃	6-CH ₃	H	CH ₃	OCH ₃	H	0.5
	17	5-COOCH ₃	6-CH ₃	H	CH ₃	OCH ₃	CH ₃	0.5
	18	5-COOCH ₃	6-CH ₃	H	H	OCH ₃	CH ₃	4
	x	5-COOCH ₃	6-CH ₃	H	H	H	CH ₃	4
30	x	5-COOCH ₃	6-CH ₃	H	Br	H	H	4
	6	4-CH ₃	6-CH ₃	H	CH ₃	H	CH ₃	4
35	10	4-CH ₃	6-CH ₃	H	H	OCH ₃	H	2
	x	4-CH ₃	6-CH ₃	H	H	H	H	4
	x	4-CH ₃	6-CH ₃	H	H	H	CH ₃	12

cont.

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Ex	R ¹	R ²	R ⁶	R ³	R ⁴	R ⁵	Dose μmol/kg	Effect % inhibition
5	3	5-COOCH ₃	H	H	H	CH ₃	CH ₃	4
	19	5-COOCH ₃	H	H	CH ₃	H	CH ₃	2
	20	5-COOCH ₃	H	H	CH ₃	OCH ₃	CH ₃	0.5
	x	5-COOCH ₃	H	H	H	H	CH ₃	20
	x	5-COOCH ₃	H	H	H	H	H	20
10	21	5-COCH ₃	H	H	CH ₃	OCH ₃	CH ₃	0.5
	x	5-COCH ₃	H	H	H	H	C ₂ H ₅	20
	22	5-OCH ₃	H	H	H	OCH ₃	CH ₃	
	23	5-OCH ₃	H	H	CH ₃	OCH ₃	CH ₃	0.5
	x	5-OCH ₃	H	H	H	CH ₃	H	20
15	24	5-CH ₃	H	H	CH ₃	OCH ₃	CH ₃	0.5
	x	5-CH ₃	H	H	H	H	CH ₃	4
20	25	H	H	H	CH ₃	OCH ₃	CH ₃	0.5
	x	H	H	H	H	H	H	4
	28	5-COOCH ₂ H ₅	H	H	CH ₃	OCH ₃	CH ₃	0.5
	26	5-Cl	H	H	CH ₃	OCH ₃	CH ₃	0.5
	27	5-CH ₃	H	H	H	OCH ₂ H ₄ OCH ₃	H	0.5
25	29	5-COOCH ₃	H	CH ₃	CH ₃	H	CH ₃	0.5
								40

x denotes a previously known compound

25

Example 35

A syrup containing 2 % (weight per volume) of active substance was prepared from the following ingredients:

30

2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]-
-(5-acetyl-6-methyl)benzimidazole · HCl 2.0 g

Saccharin 0.6 g

Sugar 30.0 g

35

Glycerin 5.0 g

Flavouring agent 0.1 g

Ethanol 96 % 10.0 ml

Distilled water (sufficient to obtain a final
volume of 100 ml)

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 5 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

10 Example 36

2-[2-(3,4-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10 % solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 20 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

25 Granules were prepared from 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-5-acetyl-6-methyl)benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), 30 and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a 10 % alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %), and dyestuff (0.2 %). Talc and powdered sugar were used for 35 powdering after the first five coatings. The coating was then covered with a 66 % sugar syrup and polished with a solution of 10 % carnauba wax in carbon tetrachloride.

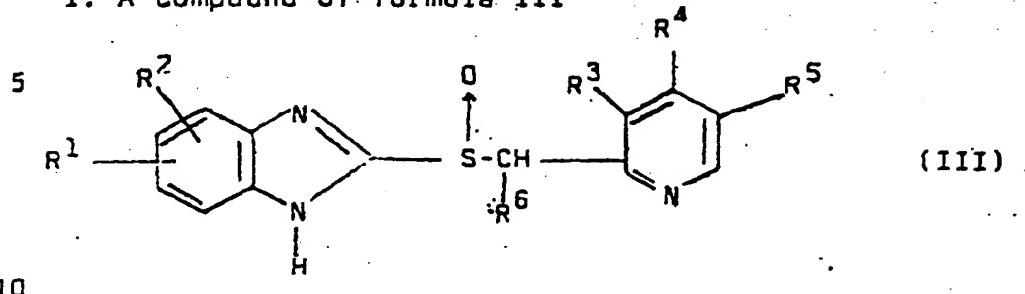
Example 38

2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-[5-acetyl-6-methyl]benzimidazole hydrochloride (1 g), sodium chloride 5 (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Claims

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1. A compound of formula III



10

or a therapeutically acceptable salt thereof in which
 R¹ and R² are the same or different and are selected
 15 from the group consisting of hydrogen, alkyl, halogen,
 carbomethoxy, carboxy, alkoxy, and alkanoyl in any
 position, R⁶ is selected from the group consisting of
 position, R⁶ is selected from the group consisting of
 hydrogen, methyl and ethyl, R³, R⁴, and R⁵ are the
 same or different and are each selected from the group
 20 consisting of hydrogen, methyl, methoxy, ethoxy,
 methoxy-ethoxy and ethoxy-ethoxy whereby R³, R⁴, and R⁵
 are not all hydrogen, and whereby when two of R³, R⁴,
 and R⁵ are hydrogen, the third of R³, R⁴, and R⁵ is
 not methyl.

25

2. A compound according to claim 1, wherein R¹ and R²
 are same or different and are each selected from the
 group consisting of hydrogen, alkyl, carbomethoxy,
 alkoxy, and alkanoyl in any position, whereby R¹ and
 30 R² are not both hydrogen, R⁶ is hydrogen, and R³, R⁴,
 and R⁵ are the same or different and are each selected
 from the group consisting of hydrogen, methyl, methoxy,
 and ethoxy, whereby R³, R⁴, and R⁵ are not all hydrogen
 and whereby when two of R³, R⁴, and R⁵ are hydrogen,
 35 the third of R³, R⁴, and R⁵ are not methyl.

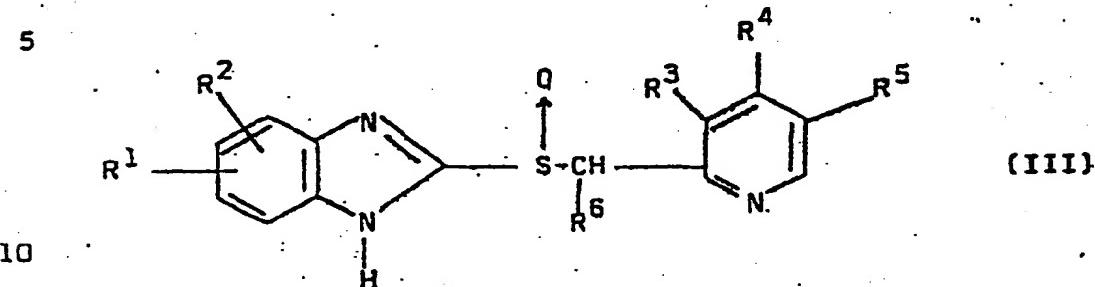
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3. A compound according to claim 1, wherein R¹, R², and R⁶ have the meanings given and R³ and R⁵ are methyl and R⁴ is methoxy.
- 5 4. A compound according to claim 1, wherein R¹, R², and R⁶ have the meanings given, R⁴ is methoxy, and R³ is hydrogen and R⁵ is methyl, or R⁵ is hydrogen and R³ is methyl.
- 10 5. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R¹, R², and R⁶ have the meanings given, R³ and R⁵ are hydrogen, and R⁴ is methoxy, ethoxy, methoxymethoxy or ethoxy-ethoxy.
- 15 6. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R¹, R², and R⁶ have the meanings given, and R³, and R⁵ are methyl and R⁴ is hydrogen.
- 20 7. A compound according to claim 1 and selected from the group consisting of.
2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-5-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
25 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
30 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
35 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

- 5 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-
-benzimidazole
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)
-benzimidazole
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-
10 acetyl-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-
-6-methyl)-benzimidazole,
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-
-6-methyl)-benzimidazole.
15 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-
methyl)-benzimidazole,
2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-
methyl)-benzimidazole,
2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-
20 methoxy-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-
methoxy-6-methyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbo-
methoxy-6-methyl)-benzimidazole,
25 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-
-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-
methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-
30 acetyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-
-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-
-methoxy)-benzimidazole,
35 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-
methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzi-
midazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-
40 chloro)-benzimidazole

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8. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound of formula III



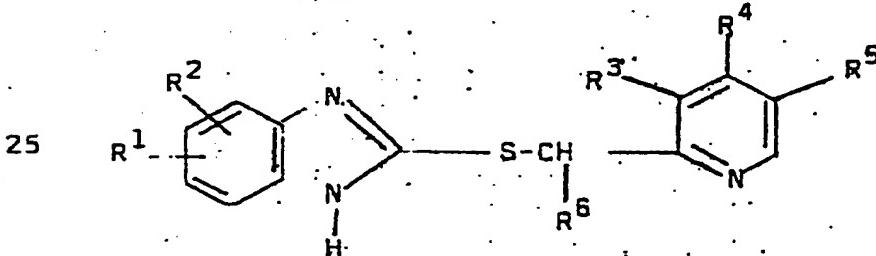
or a pharmaceutically acceptable non-toxic acid addition salt thereof in a therapeutically effective amount in which R¹ and R² are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alk酰oyl in any position, R⁶ is selected from the group consisting of hydrogen, methyl, and ethyl R³, R⁴, and R⁵ are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy, and ethoxy-ethoxy whereby R³, R⁴, and R⁵ are not all hydrogen, and whereby when two of R³, R⁴, and R⁵ are hydrogen, the third of R³, R⁴, and R⁵ is not methyl.

- 25 9. A pharmaceutical preparation according to claim 8 wherein the active ingredient is selected from the group consisting of

- 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
- 5 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
- 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 10 2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 15 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzi-
20 midazole,
- 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 25 2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
- 30 2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-
methoxy-6-methyl)-benzimidazole,
- 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbo-
methoxy-6-methyl)-benzimidazole,
- 35 2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbo-
methoxy-6-methyl)-benzimidazole,

- 2-[2-(3,5-dimethyl)-pyridylmethysulfinyl]-(5-carbomethoxy)-benzimidazole,
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-(5-carbomethoxy)-benzimidazole,
 5 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-(5-acetyl)-benzimidazole,
 2-[2-(4-methoxy-5-methyl)-pyridylmethysulfinyl]-(5-methoxy)-benzimidazole,
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-(5-methoxy)-benzimidazole,
 10 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-benzimidazole,
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-(5-methyl)-benzimidazole,
 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-benzimidazole,
 15 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethysulfinyl]-(5-chloro)-benzimidazole,
 or a pharmaceutically acceptable non-toxic addition salt thereof.

20 10. Intermediates of the formula



- 30 wherein R¹ and R², preferably in 3 to 5 position, are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R⁶ is selected from the group consisting of hydrogen, methyl, and ethyl, and R³, R⁴, and R⁵ are the same or different and are selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R³, R⁴, and R⁵



European Patent
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EUROPEAN SEARCH REPORT

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Application number

EP 79 85 0022

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL ^I)
			C 07 D 403/12 A 61 K 31/44
A	<u>DE - A - 2 548 340 (AB HASSLE)</u> * pages 1 to 12 * -----	1, 24	
TECHNICAL FIELDS SEARCHED (Int.Cl.)			
C 07 D 403/12 A 61 K 31/44			
CATEGORY OF CITED DOCUMENTS			
<p>X: particularly relevant A: technological background O: non-written disclosure P: Intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p>			
<p>N The present search report has been drawn up for all claims</p>			
Place of search The Hague	Date of completion of the search 18-07-1979	Examiner	DE BUYSER